Cleveland Clinic
Clinical Rx Forum
From the Department of Pharmacy

November/December Issue 2015, Volume 3, Issue 6

In This Issue

Cleveland Clinic
Clinical Rx Forum

From the Department of Pharmacy
Drug Information Service
(216) 444-6456, option #1

Comprehensive information about medications, biologics, nutrients, and drug therapy

Gardasil® 9: A New Vaccine for HPV Protection

By: Erica Davidson, Pharm.D.

Introduction: Human papillomavirus (HPV) is the most common sexually transmitted disease in the United States.[1] There are an estimated 79 million people infected, with 14 million new infections each year among those 15-59 years old. Most infections are asymptomatic, and 90% of people clear the infection within 2 years. However, persistent HPV infection can cause cancers and other complications. Between 2006 and 2010, 33,160 HPV-associated cancers were diagnosed, 62% in females and 38% in males. In December 2014, the Food and Drug Administration (FDA) approved Gardasil®9 (Merck and Co., Inc.), a new vaccine to prevent HPV infection.[2,3]

HPV Types and Complications: Human papillomavirus is a double-stranded DNA virus.[1] Approximately 150 types have been identified. Of the many HPV types, some are considered low risk.[1] These can cause low-grade cervical cell changes, genital warts, and respiratory papillomatosis. There are also high-risk types that can cause pre-cancerous cell changes and cancers. The complications caused by different HPV types are found in Table 1. Types that most commonly cause cancers are HPV 16 and 18, however HPV 31, 33, 45, 52, and 58 can as well.[3]

Table 1: Complications by HPV Type[3]

Complication	Percentage Caused by HPV Type
Any Invasive Cancer*	64% HPV 16,18 10% HPV 31,33,45,52,58
Cervical Cancer	66% HPV 16,18 15% HPV 31,33,45, 52,58
Anogenital Warts	~90% HPV 6,11

HPV=Human Papillomavirus
*Including cervical, vulvar, vaginal, anal, oropharyngeal, and penile cancers

(Continued on page 2)

Novel Agent for Dabigatran Reversal

By: Nick Patykiewicz, Pharm.D.

Background: Dabigatran etexilate mesylate (Pradaxa®; Boehinger Ingelheim) is an oral direct thrombin inhibitor that binds reversibly to the active site of both free and clot-bound thrombin. Dabigatran is approved by the Food and Drug Administration (FDA) for prevention of stroke in patients with nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism (VTE).[1] The RE-LY trial demonstrated that treatment with dabigatran in patients with atrial fibrillation reduces the risk of stroke with a better safety profile compared with warfarin.[2] Despite having a wider therapeutic window, rapid onset of action, shorter half-life, and a better bleeding profile when compared to warfarin, dabigatran carries a major risk for patients who have life-threatening bleeding that is uncontrollable with supportive measures. For these patients, the Cleveland Clinic Main Campus oral anticoagulant reversal algorithm recommends that patients receive FEIBA® 50 units/kg and contact nephrology for

(Continued on page 3)

(Continued from page 1)

HPV Vaccines: With the addition of Gardasil®9, there are now three vaccines available for preventing this infection: bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV).[3] These are all recombinant vaccines made from virus-like particles of the viral capsid. It is important to note that only Gardasil®9 covers cancer-causing HPV 31,33,45,52, and 58. Characteristics of each HPV vaccine are compared in Table 2.

Table 2: HPV Vaccine Comparison[3]

Vaccine	Brand Name	Viral Types Covered
2vHPV	Cervarix®*	16,18
4vHPV	Gardasil®†	6,11,16,18
9vHPV	Gardasil®9†	6,11,16,18,31,33, 45,52,58

HPV=Human papillomavirus v=valent
*GlaxoSmithKline
†Merck and Co., Inc

ACIP Recommendations: The Advisory Committee on Immunization Practices (ACIP) currently recommends HPV vaccination in 11-12 year olds for both genders, and in females 13-26 years old and males 13-21 years old who have not yet completed the series.[3] Additional groups who should be vaccinated through 26 years of age are men who have sex with men and immunocompromised patients. The ACIP recommendations differ from the FDA-approved age ranges for 9vHPV, which include females 9 to 26 years old and males only 9 to 15 years old.[2] However, a request to extend the indication to males 16-26 years old has been submitted to the FDA.[4] The ACIP recommendations state that 9vHPV, 4vHPV, or 2vHPV can be used for vaccinating females while the 9vHPV or 4vHPV can be used for vaccinating males and immunocompromised persons.[3] Any available product can be used to continue a series that has already started. At this time, the need for a booster with 9vHPV after completion of the series with either 2vHPV or 4vHPV is unknown.[4]

Safety and Interactions: In clinical trials, 9vHPV was generally well tolerated.[2,3] The safety profile was similar to that of 4vHPV, although there were more cases of mild to moderate injection-site reactions. The immune response to 9vHPV may be reduced in patients taking immunosuppressive therapies.[2] Concomitant use of 9vHPV with quadrivalent meningococcal conjugate vaccine and tetanus, diphtheria, acellular pertussis vaccine was studied and the immune response was found not to decrease for any of the vaccines.[3]

Dosing and Administration: Gardasil®9 should be administered intramuscularly into the upper arm or anterolateral thigh for a three-dose series at months 0, 2, and 6.[2,3] It is contraindicated in those with a history of hypersensitivity to any vaccine component or to yeast. According to ACIP, vaccination is not recommended during pregnancy, although the manufacturer labels it as pregnancy category B. Regardless of vaccination status, cervical cancer screening is recommended in all women 21-65 years old.[3]

Formulary Status: Gardasil®9 is currently available on the CCHS Formulary restricted to outpatient use in adults. There are no restrictions for pediatric patients. Because the use of Gardasil®9 in males 16-26 years old is considered off-label and therefore, unlikely to be covered by insurance, the 4-valent Gardasil® will remain on the CCHS Formulary.

References:

1. Markowitz LE, Dunne EF, Saraiya M, Chesson HW, Curtis CR, Gee J, et al.; Centers for Disease Control and Prevention. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2014;63(5):1-30.
2. Gardasil®9 [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; Dec 2014.
3. Petrosky E, Bocchini JA, Hariri S, Chesson H, Curtis CR, Saraiya M, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. MMWR 2015;64 (11):300-4.
4. Gardasil®9 [data on file]. Whitehouse Station, NJ: Merck & Co., Inc.; Dec 2014.

(Continued from page 1)
possible dialysis. Although hemodialysis is recommended for the elimination of dabigatran and preclinical evidence suggests coagulation factor concentrates may also reverse bleeding, there is a clinical need for a specific antidote for dabigatran.[3-5]

Novel Reversal Agent: Idarucizumab (Praxbind®; Boehinger Ingelheim) was recently FDA-approved for the reversal of the anticoagulant effects of dabigatran. Structurally, idarucizumab is a humanized mouse monoclonal antibody fragment (Fab), which binds both free and thrombin-bound dabigatran at an affinity more than 300-fold higher than the affinity of dabigatran for thrombin. Idarucizumab has a volume of distribution of 8.9 L (significantly smaller compared to dabigatran) and has a half-life of 47 minutes.[6,7]

Key Clinical Trial: Preliminary results from an analysis of the Phase III study of the Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD) demonstrated efficacy and safety measures of idarucizumab.[7] This ongoing, multicenter, prospective cohort study recruited 90 patients to receive 5 grams of intravenous idarucizumab, administered as two 50 ml bolus infusions, each containing 2.5 grams of idarucizumab. Patients were enrolled into two groups based on whether they had uncontrollable or life-threatening bleeding judged by the treating clinician (n=51) or required surgery or invasive procedures that could not be delayed (n=39). The primary endpoint of maximum percentage reversal of anticoagulant effect of dabigatran, as assessed by both dilute thrombin time (dTT) and ecarin clotting time (ECT), was demonstrated by 100% in both groups (95% CI, 100 to 100). Of the patients who had blood samples available, the secondary endpoint revealed normalization of dTT in 98% of patients in group A and 93% in group B (n=40 and n=28, respectively) and normalization of ECT in 89% of patients in group A and 88% in group B (n=47 and n=34, respectively). Serious adverse events did occur among 20% of study participants, including 18 deaths, however, these appeared to be related to an index event or associated with coexisting conditions. Overall, the authors concluded that idarucizumab rapidly and completely reversed the anticoagulation activity of dabigatran in 88% to 98% of the patients.

Clinical Utility: Idarucizumab is supplied as two single-use vials each containing 2.5 grams/50 mL, and is given as two consecutive infusions or bolus injections by administering both vials consecutively one after the other. Regardless of dabigatran demonstrating a better bleeding profile than warfarin, the lack of specific antidote previously posed a challenge in many clinical scenarios. The results from the REVERSE-AD trial have led to the FDA-approval of a novel agent for the reversal of the anticoagulant effects of dabigatran. Although idarucizumab has a significant clinical application, patient outcomes are still dependent on the anatomical and physiological nature of the bleed.

Formulary Status: Idarucizumab was recently added to the CCHS Formulary. The reversal algorithms will be updated to reflect that idarucizumab is the reversal agent for dabigatran.

References:

1. Pradaxa (dabigatran etexilate mesylate) capsules [prescribing information]. Ridgefield (CT). Boehringer Inhelgeim Pharmaceuticals, Inc. 2015 Oct.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
3. Van Ryn J, Stangier J, Haertter S, Liesenfeld K, Wienen W, Feuring M, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103(6):1116-27.
4. Pragst I, Zeitler SH, Doerr B, Kaspereit FJ, Herzog E, Dickneite G, et al. Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. J Thromb Haemost. 2012;10(9):1841-48.
5. Zhou W, Schwarting S, Illanes S, Liesz A, Middelhoff M, Zorn M, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke. 2011;42(12):3594-99.
6. Praxbind (idarucizumab) injection [prescribing information]. Ridgefield (CT). Boehringer Inghelgeim Pharmaceuticals, Inc. 2015 Oct.
7. Pollack C Jr, Reilly P, Eikelboom J, Glund S, Verhamme P, Bernstein R, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373:511-20.

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Cangrelor (Kengreal®)	Antiplatelet	Antiplatelet Therapy prior to Cardiac Catheterization	Restriction: Restricted to Interventional Cardiology for use in the Cardiac Catheterization Lab for STEMI or NSTEMI patients not adequately treated with an oral $P2Y_{12}$ inhibitor or in situations where pretreatment is not done.
Cinryze®	C1 Esterase Inhibitor	HAE ACE-Inhibitor-induced angioedema	Restriction: Restricted to 1) the Department of Allergy and Immunology for HAE and 2) for patients with ACE-Inhibitor-induced angioedema.
Diclofenac Topical Patch (Flector®)	Analgesic	Pain Control	Restriction: Restricted to Pain Management.
Fluticasone furoate and vilanterol (Breo® Ellipta®)	Respiratory Agent	COPD/Asthma	No restrictions
Idarucizumab (Praxbind®)	Antidote	Dabigatran reversal	Restriction: The first dose of idarucizumab is not restricted, but should be used according to the CCHS Anticoagulant Reversal Protocol. A Hematology Consult is required prior to administration of a second dose.
Imipenem and Cilastatin (Primaxin®)	Antibiotic	Nontuberculosis mycobacterial and *Nocardia* spp. infections	Restriction: Restricted to the Department of Infectious Diseases for the treatment of nontuberculosis mycobacterial infections and *Nocardia* spp.
Talimogene (Imlygic®)	Antineoplastic Agent	Melanoma	Restriction: Restricted to the Department of Hematology and Medical Oncology for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. To be used on Main Campus only. Restricted to adult outpatients.
Umeclidinum and Vilanterol (Anoro Ellipta®)	Respiratory Agent	COPD	No restrictions

ACE=Angiotensin-converting enzyme COPD=Chronic obstructive pulmonary disease HAE=Hereditary angioedema
NSTEMI=Non-ST segment elevation myocardial infarction STEMI=ST segment elevation myocardial infarction

Modifications to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Modifications**
Aripiprazole Extended-Release Injection (Abilify Maintena®)	Antipsychotic	Schizophrenia	Modification: Restricted to the Department of Psychiatry for initiation of therapy. Continuation of therapy is not restricted.
Clozapine (Clozaril®)	Antipsychotic	Psychotic Disorders	Modifications: 1) Restrict clozapine to certified prescribers based on requirements of the REMS program. 2) Creation of an order panel within Epic to order an ANC whenever clozapine is prescribed.
Ticagrelor (Brilinta®)	Antiplatelet	ACS	Modification: 1) The 60 mg dose was added as a line item extension.

ACS=Acute coronary syndrome ANC=Absolute neutrophil count REMS=Risk evaluation mitigation strategies

Deletions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Collagenase topical (Santyl®)	Debriding Agent	Debridement of pressure ulcers	Other more cost-effective therapies are available
Hyoscyamine, atropine, scopolamine, and phenobarbital (Donnatal®)	Antispasmodic Agent	Gastrointestinal Disorders	Other therapies are available

Deletion to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Hyoscyamine, atropine, scopolamine, and phenobarbital (Donnatal®)	Antispasmodic Agent	Gastrointestinal Disorders	Other therapies are available

Changes in Restrictions and New Therapeutic Interchange in the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Acetaminophen IV (Ofirmev®)	Analgesic	Pain Control Patent Ductus Arteriosus	Restriction: Add new restriction to include patent ductus arteriosus closure. All of the following criteria must be met: 1. Patient is unable to receive non-steroidal anti-inflammatory drugs. 2. Patient is NPO. 3. Must be ordered by an Attending Physician.
Fosaprepitant Dimeglumine IV (Emend®)	Antiemetic	Chemotherapy-induced nausea and vomiting	Restriction: Restriction is modified to include both the Department of Pediatric Hematology/Oncology and Pediatric BMT for the prevention of chemotherapy-induced nausea and vomiting from highly-and moderately-emetogenic chemotherapy. Comment: The following dosing will be used in pediatric patients: 1. Patients weighing ≥ 30 kg receive 150 mg/dose 2. Patients weighing < 30 kg receive 3 mg/kg/dose
Desvenlafaxine (Khedezla®, Pristiq®)	SNRI	Antidepressant	Therapeutic Interchange: All orders for desvenlafaxine fumarate (Khedezla®) will be converted to desvenlafaxine succinate (Pristiq®). The dose conversion from Khedezla® to Pristiq® is a one-to-one conversion

BMT=Bone marrow transplant SNRI=Serotonin norepinephrine reuptake inhibitor IV=Intravenous